Translation

PCT/CH2003/000666

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference R62627PC	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CH2003/000666	International filing date (*day/month/year*) 13 October 2003 (13.10.2003)	Priority date (*day/month/year*) 14 October 2002 (14.10.2002)
International Patent Classification (IPC) or national classification and IPC C07K 14/54		
Applicant F. HOFFMANN-LA ROCHE AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11 May 2004 (11.05.2004)	04 November 2004 (04.11.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/CH2003/000666

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-43, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages 1-38, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:
pages 1/12-12/12, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
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III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-38

because:

☒ the said international application, or the said claims Nos. 27, 28 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. _____ are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-38 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box III.1.

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The applicant is advised that claims or parts of claims relating to inventions in respect of which no international search report (ISR) has been established cannot normally be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched.

   As already mentioned in the ISR, the search in relation to the current claims 1 to 38 was directed to the parts of the claims that appear to be clear, supported or disclosed, that is the parts concerning the fusion proteins that contain an IL-15 with the amino acid sequence defined in SEQ ID NO:1.

   Since the International Examining Authority shares the opinion of the International Searching Authority, the international preliminary examination was restricted to this searched subject matter defined above.

2. Claims 27 and 28 relate to subject matter which, in the opinion of this Authority, falls under PCT Rule 67.1(iv). Consequently, no expert opinion has been established in respect of the industrial

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Box III.1.

applicability of the subject matter of said claims (PCT Article 34(4)(a)(i)).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.
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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-38 (as far as examined)	YES
	Claims		NO
Inventive step (IS)	Claims	1-38 (as far as examined)	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-26, 29-38	YES
	Claims		NO

2. Citations and explanations

1. Reference is made to the following documents:

D1: PETTIT DEAN K ET AL: JOURNAL OF BIOLOGICAL CHEMISTRY, Vol. 272, No. 4, 1997, pages 2312-2318

D2: ZHENG X X ET AL: JOURNAL OF IMMUNOLOGY, 163, No. 7, 1 October 1999 (1999-10-01), pages 4041-4048

D3: RUECKERT R ET AL: EUROPEAN JOURNAL OF IMMUNOLOGY, WEINHEIM, DE, Vol. 28, No. 10, October 1998 (1998-10), pages 3312-3320

D4: WO 97/41232 A (BETH ISRAEL HOSPITAL) 6 November 1997

2. **Clarity and support from the description** (PCT Articles 5 and 6):

The current **claims 1 to 38** relate to a fusion protein that is characterised only by a desirable characteristic or property, namely that it contains a wild-type IL-15, since the amino acid sequence of the wild-type IL-15 is not defined. The claims are therefore unclear, since the amino acid sequence is an essential feature of the invention.

2.2 As already mentioned in the application, it is totally surprising that a fusion protein consisting of a wild-type IL-15 and an Fc fragment has an antagonistic effect. Thus, for example, the results in example 5 contradict the results shown by Zheng et al. (document D2) and Rueckert et al. (document D3, which discloses the subject matter of the disclaimer).

When an invention is based on a surprising effect, the features that produce that effect must be part of the claimed subject matter. Since the application discloses only one fusion protein with this property (namely wild-type IL-15-mIgG2a with the amino acid sequence defined by SEQ ID NO:5) and does not indicate why this fusion protein has this effect and similar, known fusion proteins do not, it is not clear to a person skilled in the art what other fusion proteins could have this effect.

Consequently, there is no basis for generalising this example and the subject matter of **claim 1** is supported only insofar as it relates to a fusion protein with the amino acid sequence defined by SEQ ID NO:5 and should be restricted accordingly.

2.3 The applicant should note that the European examining procedure does not allow disclaimers for embodiments which do not solve the problem of interest ("non-working embodiments"; see G0001/03, reasons for decision, paragraph 2.5).

2.4 **Claims 23 to 25**, which are directed to a second medical indication, are inadmissible under PCT Article 6. The therapeutic application is defined

in functional terms by an active mechanism ("IL-15-mediated events") which does not allow any practical application in the form of a defined actual treatment of a pathological illness (disease).

In addition, in respect of these claims, as well as **claim 26**, the use of human or animal tissue or of a human or animal organ is not supported by the description (PCT Article 5).

2.5 **Claim 30** does not meet the requirements of PCT Article 6 because the subject matter for which protection is sought is not clearly defined. The claim attempts to define the subject matter in terms of the result to be achieved (i.e. steps b) and c)), but in so doing merely states the problem to be solved, without specifying the technical features needed to achieve this result.

In addition, step 4 is not restricted to *in vitro* treatment and therefore the claim also covers an *in vivo* treatment method.

2.6 The PCT Contracting States do not have uniform criteria for assessing the industrial applicability of **claims 27 and 28** in their present form. Patentability may also depend on the wording of the claims. The EPO, for example, does not recognise the industrial applicability of claims to the medical use of a compound; it may, however, allow claims to the first medical application of a known compound or to the use of such a compound in the manufacture of a drug for a new medical application.

3. **Novelty and inventive step** (PCT Article 33(2) and (3))

3.1 Insofar as it has been examined, the subject matter of **main claim 1** is novel.

3.2 Since the prior art does not indicate that a wild-type-IL-15-mIgG2a fusion protein would have an antagonistic effect, the subject matter of **main claim 1**, insofar as it is restricted to this fusion protein, is inventive.

4. **Additional observations:**

4.1 **Claims 17, 18 and 32** cover embryonic stem cells and **claim 21** covers parts of the human body. In the opinion of this IPEA, these claims are contrary to public order and morality and are therefore not acceptable.